

REMARKS

Claims 14, 16-26, and 28-30 were previously pending. These claims were rejected in the Office Action dated July 29, 2005. Claims 14, 15-23, and 25-28 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims at a later time. New Claims 31-36, all of which depend from Claim 24, have been added. Thus, Claims 24, 29, and 30-36 are currently pending. Claim 24 has been amended to provide proper antecedent basis for the phrase "chimeric polypeptide." Claim 24 has also been amended to explicitly define some of the conditions and to remove the reference to the term "biological response." Support for the amendment can be found in the specification and claims, for example, Claims 24 and 25 and page 17 of the specification. Claims 29 and 30 have been amended in light of the amendments to Claim 24. Support for these amendments can be found in the original claims and the specification. Support for the new claims can be found throughout the original specification and claims. For example, support can be found on page 18, second full paragraph and last paragraph, Claims 16 and 17, SEQ ID NO: 2, and Figure 6. No new matter has been added by these amendments.

Applicants request the insertion of the above particular priority paragraph into the specification. Applicants note that a request for a corrected filing receipt, noting the above information and requesting correction of the previous filing receipt in line with the above information, was filed January 12, 2002. However, Applicants have not had a response regarding this request yet. Applicants note that the above priority information was previously provided to the Patent Office and that it was acknowledged by the Patent Office in the Notification of Acceptance of Application Under 35 U.S.C. 371, mailed 12/04/97. Additionally, Applicants note that a Petition was filed on November 25, 1998 requesting the deletion of Nancy Levin as an inventor; however, Applicants have not received any indication that their petition has been accepted.

Applicants appreciate the consideration of the previously submitted references and the withdrawal of the rejection of Claims 24-26 under 35 U.S.C. §112. Claim 26 has been cancelled.

Reconsideration of the pending rejections in view of the above amendments and following remarks is respectfully requested.

Rejection under 35 U.S.C. §112

Claims 24-26, 29, and 30 stand rejected under 35 U.S.C. §112, first paragraph, as failing to “provide enablement for 1) a method of treating a condition associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by an OB receptor, or 2) a composition for the treatment of obesity.” Of the rejected claims, only Claims 24, 29, and 30 are currently pending. The Office Action states that this is a scope of enablement rejection. The nature of this rejection was affirmed in the Examiner interview.

As discussed during the interview, a large amount of the scope of enablement rejection stemmed from the use of the terms “condition” and “biological response.” Applicants have amended Claim 24 to remove these terms and to more specifically define the particular condition being treated. As such, Applicants submit that many of the issues regarding the rejection have been addressed. However, Applicants supply the following comments to further demonstrate that the claims are adequately enabled.

Applicants note that some of the statements in the Office Action are incorrect regarding the effectiveness of leptin on non-ob/ob mutant organisms. In the Office Action, it was asserted that the OB protein only works on ob/ob mutants. The Examiner referred to Gale et al. (Recent Advance in Nutritional Sciences, 134:295-8, 2004) as suggesting that administration of leptin to patients with elevated leptin levels may not always be effective due to leptin resistance. Furthermore, Bell-Anderson was asserted as noting that there was variation in amount of weight loss that resulted from the administration of leptin. Applicants note that neither of the cited references actually asserts that any amount of leptin cannot have some impact on weight loss or obesity. Rather, the references appear to suggest that not everyone will have all of their weight permanently reduced when leptin is administered at certain levels and in certain manners. Applicants note that one reason that the above references may have characterized the effects of leptin as such is that, as noted below, lower levels of leptin (or less efficient versions of leptin) are likely to have been used in the references discussed by Bell and Gale. Moreover, these references might also be referring to finding a “magic-bullet” type treatment, where a single dose of the protein results in permanent and large decreases in weight for all people. Applicants are not claiming such impressive results, and are merely asserting that the claimed method results in some weight loss, at some point, for some amount of time.

More importantly, the above interpretation of the cited references is directly rebutted by the information in the present application, which demonstrates that OB protein can work as desired, even when it is not in an ob/ob background. Applicants direct the Examiner to page 20, lines 29-33 and Figure 1 of the present application, which demonstrate the effectiveness of administering OB to lean (*i.e.*, non ob/ob) mice. Thus, it is clear from the specification itself that organisms without the ob/ob mutation, including lean subjects, are clearly influenced by the administration of leptin. Moreover, Applicants note that their chimeric form of the protein is superior to the native form of leptin, and thus, provides for an even greater advantage.

Moreover, the above references do not cast significant doubt on the currently claimed method (*e.g.*, Bell only notes that “there was considerable variability,” rather than stating it did not work). While the above references are only tangentially relevant to the assertion of whether leptin will work (as they are general review articles and refer to particular forms or methods of use), Applicants note that not only their data, but also extrinsic references have clearly demonstrated that leptin works on normal (non-ob/ob mutants) animals. For example, Rosenbaum et al. (*J. Clin. Endro. & Metab.*, 87::2391-2394, 2002) notes that not only does leptin reduce weight loss in leptin-deficient rodents and humans, but it can also reduce weight in “leptin-sufficient animals and humans...” (p. 2391, second full paragraph). Applicants note that the amount of leptin required to achieve this is approximately 10 fold the normal amount, for normal leptin (of course, it should be less for the Applicant’s chimeric leptin, as described below). There are additional references which demonstrate that leptin, when given in sufficient levels, does induce weight loss in leptin-sufficient animals. (*See also*, Campfield et al. 1995, *Sci.*, 269:546-48; Campfield et al., *Sci.* 280:1383-1387 (1998)(“[i]t also causes reduction of food intake and body weight when administered to lean mice, rats, and monkeys” citing Campfield et al., *Horm. Metab. Res.*, 28:619; *Endocrinol. Metab.*, 4:81, 1997)). Thus, while the amount of OB protein required to induce the recited effects can be larger for some non-ob/ob animals, it is clear that, when given an appropriate, or “therapeutically effective amount,” that the desired results will occur. We note that this is shown in Heymsfield et al. (Recombinant Leptin for Weight Loss in Obese and Lean Adults, *JAMA*, 282:1568-1575 (1999)), a copy of which is enclosed). What is apparent is that the references cited by the PTO are likely not to have administered a therapeutically effective amount of the compound.

Additionally, Applicants note that the mere fact that something is leptin-resistant does not mean that they are leptin nonresponsive. Leptin resistance merely implies that increases in leptin do not result in as large a response as might otherwise be expected. Thus, administration of leptin to leptin-resistant individuals will simply require additional leptin to see the desired result. Applicants note the idea of “resistance” in science is common and does not typically denote absolute immunity. For example, type II diabetics are insulin-resistant, however, treatment of these individuals still involves insulin and actually involves administration of more insulin than would be given to an individual who is not insulin-resistant. Thus, “resistance” does not denote that leptin cannot work; it merely suggests that additional amounts of leptin (or more potent forms of leptin) are required to achieve the desired result.

Applicants respectfully remind the Examiner that “[o]ffice personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 U.S.P.Q. 193 (C.C.P.A. 1963); *In re Langer*, 503 F.2d 1380, 183 U.S.P.Q. 288 (C.C.P.A. 1974))” (M.P.E.P. § 2107.03). As noted above, there is current data on mice, monkeys, and humans, which demonstrate that the claimed method does work. This is more than sufficient to meet the standard for patentability.

Regarding the ability of chimeric leptin to treat bulimia, Applicants note that, as demonstrated by the present application, the level of leptin in bulimic patients is not, *per se*, relevant to whether or not leptin can be used to impact or alter a patient’s characteristics. As noted above, when leptin is administered to mice with normal leptin levels, it still produces the desired results in those mice, even if their leptin levels are “normal.” In light of these results, the fact that leptin levels could be “normal” in some bulimic patients is irrelevant, as leptin clearly has the desired impact, even in non-ob/ob animals, where there is, presumably, a normal amount of leptin. Additionally, as noted below, there are many references, published since the filing date of the current application, which continue to establish relationships between bulimia and leptin. The abstracts of these references are being submitted herewith.. As such, Applicants submit that the references cited by the PTO in the previous Office Action are not directly relevant to the

claimed invention, and that the present application and the references submitted herewith demonstrate the Examiner's requested connection between bulimia and leptin.

As per the request in the interview, Applicants are submitting numerous references to further verify a recognized association between bulimia and leptin. For example, Jimerson et al. (*J. Clin. Endo. & Metab.*, 85:4511-4514, 2000), entitled "Decreased Serum Leptin in Bulimia Nervosa," specifically notes that the results are consistent with the idea that, "decreased leptin function may be associated with alterations in eating patterns..." (abstract). Relationships are further described in "Impact of Binge Eating on Metabolic and Leptin Dynamics in Normal Young Women" (Taylor et al., *J. Clin. Endo. & Metab.* 1999) and in "Reduced Plasma Leptin Concentrations in Bulimia Nervosa," (Brewerton et al., *Psychoneuroendocrinology*, 25:649-658 (2000)).

Applicants note that any previous showing that leptin levels remained constant in patients suffering from the disorders merely emphasizes the novelty and nonobviousness of the claims. Moreover, Applicants submit that the above amendments to the claims are believed to have resolved these issues as well. Finally, in light of the fact that even ordinary leptin can induce a visible result in OB "normal" subjects, Applicants submit that a *prima facie* case of lack of adequate enablement has not been made. In particular, Applicants note that no reason for why the claimed method would not work in a manner commensurate with the claims has been provided. As noted herein, a "normal" level of OB protein in a subject does not mean that administering OB protein will not work on the subject. In light of the above, the applicants request that the rejection be withdrawn and Claims 24, 29, and 30 be allowed. Applicants note that new Claims 31-36 depend from Claim 24 and are also adequately enabled.

Rejection under 35 U.S.C. §102(e)

Claims 24, 29, and 30 stand rejected under 35 U.S.C. §102(e) as being anticipated by Pellymounter, U.S. Patent Application Publication No. 2003/0203837, filed 5/30/2003 and claiming priority to 11/22/1995.

Claims 24, 29, and 30 have been amended. The present claims recite that the condition to be treated is bulimia. Pellymounter does not describe the treatment of bulimia. Because each of the elements in the claims has not been taught by the cited reference, Applicants request that the rejection be withdrawn and the claims allowed.

Additionally, Applicants note that, in general, they do not concede the points asserted in the Office Action and reserve the right to make further distinctions as appropriate. For example, the phrase “therapeutically effective amount” is to be interpreted in light of the claims and the specification, from the view of one of skill in the art. Furthermore, the “effective amount” refers to the condition being treated. Thus, these can provide relevant limitations to the scope of the claims. Finally, while it has been asserted that “Pellymounter teaches a method with these limitations [*i.e.*, those in Claims 29 and 30], and therefore clearly anticipates Claims 29 and 30” (page 10, first paragraph), the rejection itself does not actually indicate where or how Pellymounter teaches the limitations of Claims 29 and 30. Applicants request that, if the rejection is to be maintained, that the specific teachings in the cited art of the elements in Claims 29 and 30 be set forth in the next Office Action.

In light of the above, Applicants request that the rejection of Claims 24, 25, 29, and 30 be withdrawn and the claims allowed. Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also novel over Pellymounter.

Rejections under 35 U.S.C. §103(a)

Claims 14, 16-23, 26, and 28 stand rejected under 35 U.S.C. §103 as being obvious over Pellymounter in view of Capon et al (U.S. Pat. No. 5,455,165). As noted above, only Claims 24, 29, and 30 of the previously rejected claims are pending. These claims have not been rejected under 35 U.S.C. §103 (a). Applicants note that neither of the cited references addresses the treatment of bulimia. As all of the elements have not been taught by the combination of the references, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and the claims allowed.

Additionally, Applicants note that Capon’s publication date is October 3, 1995. Applicants note that both Capon, and the present application, were assigned to Genentech Inc.

Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also nonobvious over the cited art.

Rejections under 35 U.S.C. §103(a)

Claims 14, 16-26, and 28-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Zhang et al. (hereinafter “Zhang”), Basinski et al. (‘744 or ‘886,

(hereinafter "Basinski")), DiMarchi et al ('954 or '336, hereinafter "DiMarchi"), in view of Shin et al. (hereinafter "Shin") or Ashkenazi et al. (hereinafter "Ashkenazi"). The Examiner has asserted that one of skill in the art would 1) not have thought that leptin acted on the brain and 2) not have thought that the blood-brain barrier was a relevant problem when considering the administration of a modified leptin protein.

As noted above, only Claims 24, 29, and 30-36 are pending. These claims recite a treatment for bulimia. The cited references do not teach the claimed method for the treatment of bulimia. The claimed method is for the treatment of bulimia in a patient having the disease; the method involves both the administration of the chimeric polypeptide to the particular patient, and the administration of an effective amount of the chimeric polypeptide. As these elements are not taught in the cited references, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and the claims allowed. Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also nonobvious over the above cited combination.

Conclusion

Applicants respectfully submit that for the above recited reasons the current rejections should be withdrawn and that the present application is in condition for allowance. If, however, some issue remains, the Examiner is cordially invited to telephone the undersigned in order to resolve such issue promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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